Transient haemodynamic events in neurologically compromised infants: A simultaneous EEG and diffuse optical imaging study

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A B S T R A C T

We describe a series of novel simultaneous EEG and diffuse optical imaging studies of newborn infants. These experiments provide evidence of large, transient haemodynamic events which occur repeatedly and consistently within and across several infants with neurological damage, all of whom were diagnosed with seizures. A simple but independent process of rejecting artifacts and identifying events within diffuse optical imaging data is described, and this process is applied to data from 4 neurologically damaged neonates and from 19 healthy, age-matched controls. This method results in the consistent identification of events in three out of four of the neurologically damaged infant group which are dominated by a slow (> 30 s) and significant increase in oxyhaemoglobin concentration, followed by a rapid and significant decrease before a slow return to baseline. No comparable events are found in any of our control data sets. The importance and physiological implications of our findings are discussed, as is the suitability of a combined EEG and diffuse optical imaging approach to the study and monitoring of neonatal brain injury.

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Introduction

Brain injury in the perinatal period is a major cause of mortality and life-long neurodisability. The aetiology and pathophysiology of perinatal brain injury is complex and multifactorial. However, alterations in cerebral haemodynamics and oxygenation are implicated in many forms of brain injury of both preterm and term infants. Seizures are a common symptom of many neurological disorders, both congenital and acquired, although they are poorly classified, frequently under diagnosed, and are difficult to treat (Rennie et al., 2008). There is also growing evidence that seizures themselves can be damaging to the developing brain (Thibeault-Eybalin et al., 2009; Glass et al., 2009; Zimmermann et al., 2008; Scher, 2003).

Electroencephalography (EEG) is the gold-standard neuro-monitoring technique in cases of neonatal seizure and has many significant advantages including portability, stability and easy application (Boylan et al., 2002). However, the interpretation of EEG data obtained in the perinatal period is extremely challenging because of the high-amplitude, mixed-frequency nature of the neonatal EEG (Vanhatalo and Kaila, 2006). There have also been many reports of clinically observed neonatal seizure events (i.e. fitting) which do not exhibit a simultaneous electrographic correlate (Weiner et al., 1991; Pinto and Giliberti, 2001). These observations can only be explained if either the fitting events have a non-epileptic origin, or there is a failure in the sensitivity of scalp EEG. Although it can be improved using dense sampling and source localisation techniques, the depth sensitivity of EEG is severely limited.

Seizures in adults and children have been shown to be associated with significant haemodynamic responses using a variety of techniques (Duncan, 1997; Avery et al., 2000; Salek-Haddadi et al., 2002; Gallagher et al., 2008; Roche-Labarbe et al., 2008). A better understanding of how the neonatal cerebral vascular system reacts during and after seizure events, particularly in infants who have already suffered hypoxic injury, is highly desirable and may well have an impact on treatment (Silverstein, 2009).

The neonatal head, by virtue of its small size and thin skull, is ideally suited for interrogation by diffuse optical imaging (DOI), and clinical studies of the neonatal brain using diffuse optical techniques have been a fruitful area of research for nearly 25 years. A number of studies have successfully employed DOI as a method of imaging neonatal brain injury (Van Houten et al., 1996; Hedben et al., 2002; Austin et al., 2006), whilst many more have promoted the use of simpler diffuse optical techniques for the monitoring of neonatal cerebral haemodynamics (Wyatt et al., 1986; Cope and Delpy, 1988; Meek et al., 1999; Roche-Labarbe et al., 2010). Although maintaining adequate cerebral perfusion and oxygenation is critical in newborn infants, limitations in quantification and precision have prevented the routine clinical use of diffuse optical techniques (Sorensen and Greisen, 2006).
Diffuse optical imaging can provide both excellent temporal resolution (10 Hz is typical) and good spatial resolution (Gibson et al., 2005). Even when a planar imaging array is employed, DOI can provide accurate localisation of changes in haemoglobin concentration to a depth of up to 30 mm (Correia et al., 2009; Heiskala et al., 2009).

Although combined EEG-fMRI methods have been very successful in the study of the haemodynamics of epileptic and seizure activity in children and adults (Gotman, 2008; Vulliemoz et al., 2010), similar studies are almost impossible with critically ill newborns. Diffuse optical imaging has several advantages over fMRI. It is portable and can be brought to the cot-side of an infant in intensive care, is completely compatible with EEG and is relatively insensitive to movement artifacts. A simultaneous EEG and diffuse optical imaging (DOI) method is therefore well suited to the study of the haemodynamics of neonatal seizure, and could potentially provide an improved method of seizure diagnosis.

We have developed a paradigm which allows EEG, with the full neonatal clinical montage, to be performed simultaneously with DOI of a large proportion of the neonatal cerebral cortex. In this paper we present the results of the application of this technique to four newborn infants with perinatal brain injury, all of whom had been diagnosed with seizure. We also present DOI data recorded in a large number of age-matched controls. These EEG-DOI experiments represent a preliminary assessment of the suitability of the technique for the study of neurovascular coupling and neonatal seizure at the cot-side.

Methods

Subjects

Four infants with perinatal brain injury were recruited from the Neonatal Intensive Care Unit of The Rosie Maternity Hospital, Cambridge, UK on the basis of a clinical diagnosis of seizure. Ethical permission was obtained from the Cambridgeshire Research Ethics Committee and signed informed consent was obtained from the parents of all recruited infants. All four infants (S01–S04, median gestational age: 40 weeks, range: 4.4 weeks) had received anticonvulsant medication for the study of neurovascular coupling and neonatal seizure at the cot-side.

<table>
<thead>
<tr>
<th>Infant</th>
<th>Age at birth (weeks + days)</th>
<th>Age at seizure diagnosis (days)</th>
<th>Age at study (days)</th>
<th>Seizure form</th>
<th>Related condition</th>
<th>Drug regime</th>
<th>Ventilation</th>
<th>Experiment performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>S01</td>
<td>42+1</td>
<td>4 days</td>
<td>9 days</td>
<td>Clonic, left-sided movements. Left-sided seizure confirmed by EEG</td>
<td>Left middle and posterior cerebral artery infarct</td>
<td>Phenobarbital</td>
<td>High frequency oscillatory ventilation</td>
<td>Simplified bilateral NIRS and reduced-electrode EEG</td>
</tr>
<tr>
<td>S02</td>
<td>38+5</td>
<td>20 h</td>
<td>5 days</td>
<td>Clonic movements of legs. Flicking of eyelids and jaw</td>
<td>Suspected sepsis at birth</td>
<td>Phenobarbital, phenytoin, clonazepam infusion.</td>
<td>Conventional mechanical ventilation</td>
<td>Full EEG-OT with clinical, 9-electrode EEG montage</td>
</tr>
<tr>
<td>S03</td>
<td>38+1</td>
<td>3 days</td>
<td>6 days</td>
<td>Generalised seizures confirmed by EEG</td>
<td>Hypoglycaemia</td>
<td>Phenobarbital and clonazepam infusion</td>
<td>Conventional mechanical ventilation</td>
<td>Full EEG-OT with clinical, 9-electrode EEG montage</td>
</tr>
<tr>
<td>S04</td>
<td>38+5</td>
<td>1 day</td>
<td>13 days</td>
<td>Generalised seizures confirmed by EEG</td>
<td>Severe neonatal encephalopathy. Right temporal haemorrhagic stroke</td>
<td>Phenobarbital, phenytoin, clonazepam and midazolam infusion.</td>
<td>Conventional mechanical ventilation</td>
<td>Full EEG-OT with clinical, 9-electrode EEG montage</td>
</tr>
</tbody>
</table>

Experimental paradigm

Studies were performed using a novel dual-modality sensing array which includes 6 co-located, combined EEG electrodes and optical fibre bundles. These ‘opto-electrodes’ were described previously (Cooper et al., 2009). The sensing array consists of two sets of 5 source and 6 detector fibre bundles, providing a total of 60 DOI channels, with 30 arranged over each temporal lobe. The 22 optical fibre bundles are coupled to the subject using a silicone rubber cap, which fixes source-detector separations whilst remaining relatively flexible and naturally adhering to the scalp. The cap is held in place using a number of Velcro® straps, which can be adjusted to suit the individual infant. The array is designed so as to apply opto-electrodes at locations approximately equal to the 10–20 positions T3, C3, O1, O2, C4, and T4. The standard neonatal EEG montage is completed by applying normal EEG electrodes at F3, F4 and Cz as well as reference and ground electrodes. A diagram of the sensing array is shown in Fig. 1. In the case of infant S01, a much-simplified simultaneous EEG-DOI experiment was performed using two source-detector pairs and four electrodes arranged bi-laterally over the temporal lobes.

Optical imaging was performed using the UCL Optical Topography System as described by Everdell et al. (2005). The system can employ up to 32 laser diode sources and 16 avalanche photodiode detectors with a sample rate of 10 Hz. Sources are arranged in pairs, with each pair consisting of one 690 nm source and one 850 nm source. EEG recording was performed using a MicroMed SystemPlus clinical system (MicroMed S.p.A, Italy), sampling at 256 Hz or greater, with a band pass filter applied at 0.3–70 Hz. A 50 Hz notch filter was also applied to minimise the effect of mains interference in the electrically noisy neonatal intensive care unit. In infants S02, S03 and S04, a single-channel electrocardiogram (ECG) was also recorded, using a dedicated channel of the EEG amplifier system.

Simultaneous EEG-DOI recording was performed for between 45 and 100 min in each brain-injured subject. The length of recording was determined by the clinical condition of the infant under the supervision of the attending Neonatologist.

The control data is of three different forms. Control data sets C01 and C02 were recorded using the same optical imaging array described above, but without the addition of the EEG system and associated electrodes (i.e. optical topography data only). Control data sets C03 to C07 were recorded using a different array which interrogated the occipital lobe, and included the simultaneous recording of a limited-channel EEG. Control data sets C08 to C19 were recorded using a second UCL Optical Topography System, and although the layout of optical sources and detectors was different to that shown in Fig. 1, the positioning on the head was very similar, covering the majority of the temporal lobes. The duration of recording was decided by the attending
Neonatologist on the basis of the behavioural state of the infant. Typically, each dataset was 20–25 min in length.

Artifact and event identification

Examination of the un-processed optical data of the neurologically damaged infants revealed several large, unexplained deviations from the apparent baseline, which did not appear to be artifact related. An example of two such features is provided in Fig. 2. In order to determine a meaningful baseline for these features (which is necessary to convert raw attenuation data into changes in haemoglobin concentrations), and to determine whether they were consistent and repeated, it was necessary to develop an objective, automated approach to the identification of these events. Such an approach would then be applicable to age-matched control data, which would allow us to determine whether these features are a common occurrence in this age group or whether they are related to neuropathology.

The analysis consisted of two operations. The first was to locate and reject periods of optical topography data which were corrupted by movement artifact, and the second was to identify the features of interest. Before either of these operations was performed the dataset was pre-filtered using a band-pass Butterworth filter between 0.002 and 1.5 Hz to eliminate very slow trends in laser diode source power, high-frequency noise, and heart rate oscillations.

In order to identify periods of movement artifact, we used the following approach: The standard deviation (SDn(t)) of the 5 s of optical intensity data about each data point (t) was calculated for each source-detector pair (n). The mean standard deviation for each source-detector pair (SDn) was also calculated. Changes in total haemoglobin concentration (HbT(t)) were calculated for the entire optical data set using the mean intensity of each channel as a baseline. These data were then differentiated to give the rate of change in total haemoglobin concentration (HbT'(t)). If a given data point, for any channel, was found to occupy a data window with a standard deviation greater than x times the mean standard deviation, whilst the rate of change of total haemoglobin exceeded a threshold of y (i.e. if SDn(t) > x × SD AND HbT'(t) > y) then the 5 s of data before and after that data point, for all channels, was identified as movement corrupted. By comparison with the visual inspection of movement-corrupted data from a previous functional activation study, the final values of x and y were selected to be 4.5 (dimensionless) and 0.3 μm/s respectively.

After periods of movement artifact had been rejected, events were identified by using a variation in optical intensity from a mean – DC filtered baseline (0.002–0.005 Hz). On visual inspection the observed features appeared large (relative to background variations), slow (typically >30 s) and dominated by an increase in intensity. Therefore the identification algorithm was designed to find periods where the mean intensity over 15 s of data exceeded the baseline by 8% (of the baseline intensity) in at least one channel at one wavelength. Once an event was located, the following 100 s of data were skipped to prevent a single event being identified repeatedly. Where possible, these events were then subjected to a further rejection process based on visual inspection of the synchronised EEG data. If excessive movement was present in the EEG, the event was rejected. For infants S01–S04 and C01 and C02, this entire event identification process was performed independently for data recorded over each side of the head so that any lateralisation could be identified.

Once an event was identified, an epoch consisting of 100 s of data before and after that event position was selected. Variations in oxyhaemoglobin concentration [HbO2] and deoxyhaemoglobin concentration [HHb], and reconstructed optical images were then produced using a period prior to the identified event position as a baseline. The baseline period was selected as the average of the first 40 s of each epoch (i.e. from -100 to -60 s relative to the identified event position).

Images of the change in optical absorption were produced using a linear image reconstruction algorithm based on the Rytov approximation to the diffusion equation (Gibson et al., 2005). These images were then converted to changes in [HbO2] and [HHb] using the specific absorption coefficients reported by Matcher et al. (1995).

Results

The results of the movement and event identification procedures for four neurologically damaged infants (sample) and the 19 healthy term infants (control) are as follows: An average of 1.41% and 14.9% of DOI data were rejected due to movement artifact in the sample and control groups respectively. The average number (and standard deviation) of events identified per hour of accepted DOI data was 8.5 (6.7) for the sample group and 6.5 (4.8) for the control group. Note that a significant fraction of the 90 min of optical imaging data acquired for infant S04 was removed prior to the implementation of the processing algorithms because of the presence of a significant
consistent. Oxyhaemoglobin concentration increases significantly lower on average than that of the control infants (student t-test, \( p < 0.05 \)). This is very likely due to the various levels of sedation to which the sample infants were subjected; movement was far less common. The number of identified events per hour of non-movement-corrupted data for the sample infants is not significantly different from those of the control infants (student t-test, \( p < 0.05 \)). The events identified in infant S01 are completely lateralised, occurring only over the left hemisphere. For S02, some events were identified on both sides of head individually, and some occurred globally. Infant S03 exhibited no independent right-sided events, but several on the left and globally. Only one event was identified in infant S04, but it was rejected on the basis of movement on the EEG recording.

Data from a single selected channel showing haemoglobin concentration variations for the first event identified in infants S01 to S03 are shown in Fig. 3a–c. A selection of mean defined events, for all three infants, is shown in Fig. 4. Although the scale and duration is variable, the form of these events, both within and across infants, is remarkably consistent. Oxyhaemoglobin concentration increases significantly and reaches a peak after a mean (and standard deviation) of 26.2 (12.5) s. It then rapidly decreases, to significantly below the defined baseline, reaching a minimum after an average of 55.5 (13.3) s before slowly returning to baseline. The average total \([\text{HbO}_2]\) event duration is 103.4 (19.7) s. Deoxyhaemoglobin concentration follows a similar pattern, occurring in \([\text{HHb}]\). The right side of the head exhibited no comparable event. Again, no consistent or significant variations were observed. The EEG data from infants S01–S04 were examined by a clinical neurophysiologist experienced in neonatal EEG examination. Infants S01–S03 all exhibited some suppression of EEG amplitude and S02 and S03 were discontinuous. The EEG of infant S04 was continuous and not obviously suppressed. None of the data sets contained evidence of electrographic seizure activity. Once the optical events described above had been identified, the corresponding periods of EEG were re-examined and no consistent variation in EEG pattern could be observed in any of the infants. Where available, the ECG was converted to a measure of heart rate, which was examined during each defined event. Again, no consistent or significant variations were observed.

Discussion

These experiments are, to our knowledge, the first example of the use of full montage neonatal EEG simultaneously with diffuse optical topographic imaging. Despite failing to observe any electrographic seizure events, we have used a simple, automated approach to identify a repeated, transient haemodynamic event which is present in the diffuse increase in background noise, believed to be related to changes in ambient light conditions in the neonatal intensive care unit which were beyond our control.

The percentage of the optical topography data rejected due to movement artifact in the neurologically damaged infants is significantly lower than that of the control infants (student t-test, \( p < 0.05 \)). This is very likely due to the various levels of sedation to which the sample infants were subjected; movement was far less common. The number of identified events per hour of non-movement-corrupted data for the sample infants is not significantly different from those of the control infants (student t-test, \( p < 0.05 \)). The events identified in infant S01 are completely lateralised, occurring only over the left hemisphere. For S02, some events were identified on both sides of head individually, and some occurred globally. Infant S03 exhibited no independent right-sided events, but several on the left and globally. Only one event was identified in infant S04, but it was rejected on the basis of movement on the EEG recording.

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Fig. 4. Examples of the average of defined events. The first column shows a left- and a right-sided channel for the mean of all the left-sided events in infant S01. The second column shows a left and a right-sided channel for the mean of all left-sided events in infant S02 and the third column shows a left and a right-sided channel for the mean of all globally defined events in infant S03. The fourth column shows a left and right-sided channel for all globally defined events in control infant C01, which appear to be non-physiological in origin. The horizontal red and blue bars indicate periods of significant HbO2 and HHb change relative to the period of data from -100 to -60 s, using a two-tailed t-test with p < 0.05.

Fig. 5. An example of a series of reconstructed images of change in HbO2 concentration for a single event defined in infant S02. The series consists of 20 images, each reconstructed using the mean of 10 s of data and corresponding to a depth of 9–12 mm. This was the layer of greatest HbO2 concentration change. The time position gives the time about which each 10 s of data was centred, relative to the defined event start time.
optical data of three out of four neurologically compromised infants but is completely absent in 19 healthy, age-matched newborns.

Data sets C01 to C19 do not constitute ideal controls. Simultaneous EEG recording was only performed in C03 to C07, which interrogated a different region of the brain, and the experiments which resulted in data sets C08 to C19 were performed using a different arrangement of sources and detectors. The control group were also not subject to mechanical ventilation or sedation. However, these control data sets were sufficient to establish that these large, slow variations in haemoglobin concentrations are not a common feature of neonatal cerebral haemodynamics.

These haemodynamic events appear robust and consistent within our relatively small sample, and all evidence indicates that they are of a physiological origin. The fact that these data can be reconstructed to produce meaningful images, particularly ones which show a peak change at a cortical depth, is a particularly strong indication that these events are due to variations in cerebral haemoglobin concentrations and not due to artifact or physiological changes in superficial tissues. The absence of any events in infant S04, who was examined 12 days after the initial seizure diagnosis, was only lightly sedated and exhibited little EEG abnormality, is a further indication that these haemodynamic events are not an artifact inherent to the paradigm.

Although these events are apparently physiological, their origin is, as yet, undetermined. Without other physiological measures it is impossible to know for certain whether these events represent localised changes in cerebral blood flow and volume due to variations in neuronal metabolism, or whether they result from a failure in the brain’s ability to insulate itself from systemic changes. The fact that many of these events are lateralised, and even focal, and that (where measured) there was no associated fluctuation in heart rate, does suggest that these events have a non-systemic origin. However, it is also possible that an inhomogeneous response of localised regions of damaged tissue to a systemic change in blood pressure could give rise to such focal changes.

The haemodynamic events we have identified are consistent in their form, but they do not exhibit the variations in [HHb] which are commonly associated with a change in regional cerebral blood flow (rCBF) in adults. The classical response to functional stimulation consists of increase in [HbO2] and a concurrent decrease in [HHb], producing a positive BOLD signal (Obrig and Villringer, 2003). Studies of functional activation using BOLD-fMRI and diffuse optical techniques have shown the haemodynamic response in newborn infants to be highly variable. Whilst the functional response is still associated with an increase in rCBF, many studies have reported an increase in both oxy and deoxyhaemoglobin concentrations (Meek et al., 1998; Hoshi et al., 2000; Muramoto et al., 2002).

Although the aetiology of the brain injury was heterogeneous, the diagnosis of seizure and the application of the anti-epileptic drug phenobarbital are the only features common to all the infants in whom the diagnosis of seizure and the treatment with phenobarbital are the only common factors. These events consist of an initial increase, then dramatic fall in [HbO2] and [HHb], which can be either localised or global. Although these features show remarkable consistency in three out of four infants studied here, their incidence in brain-injured infants, and their association with particular neurological conditions and medications is beyond the limits of this study. Whether these features result from disturbances in local autoregulatory control or from continuing seizure-related neuronal activity, not visible to conventional EEG, is uncertain and warrants further investigation.

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References


